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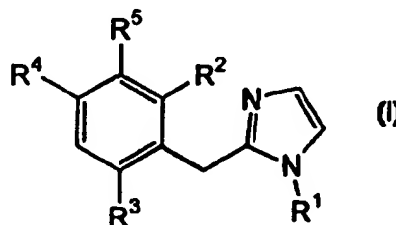
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(54) Title: IMIDAZOLES WITH SEROTONIN RECEPTOR BINDING ACTIVITY

(57) Abstract

This invention relates to compounds having serotonin receptor binding activity, to pharmaceutical compositions containing them and to their medical use, particularly in the treatment of CNS conditions. Described herein are compounds which have general formula (I), wherein R¹ is selected from H, C₁₋₆alkyl and benzyl; R² is selected from H and C₁₋₆alkyl; R³ is selected from H and C₁₋₆alkyl; R⁴ is selected from C₁₋₆alkyl and halo; R⁵ is selected from H and OH; and salts, hydrates and solvates thereof. Also described is the use of these compounds as pharmaceuticals to treat indications where stimulation of subtypes of the serotonin receptor is implicated, such as migraine.



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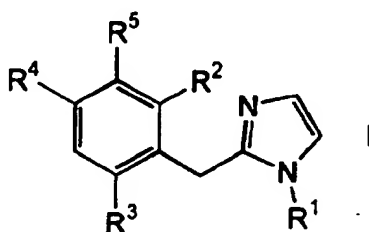
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Imidazoles With Serotonin Receptor Binding Activity

This invention relates compounds having serotonin receptor binding activity, to pharmaceutical compositions containing them and to their medical use, particularly in the treatment of CNS conditions.

According to one aspect of the invention, there are provided compounds of Formula I and salts, solvates or hydrates thereof:



10

wherein

R¹ is selected from H, C₁₋₆alkyl and benzyl;

R² is selected from H and C₁₋₆alkyl;

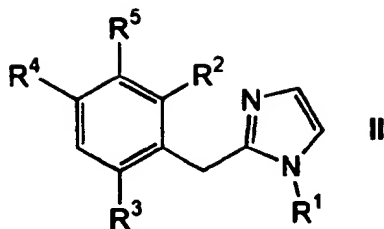
15 R³ is selected from H and C₁₋₆alkyl;

R⁴ is selected from C₁₋₆alkyl and halo;

R⁵ is selected from H and OH; and

with the proviso that when R¹ is H and R² and R³ are methyl, R⁴ is not t-butyl.

20 According to another aspect of the invention, there is provided a pharmaceutical composition comprising a compound of Formula II, in an amount effective to stimulate 5-HT_{1D}-like receptors, and a pharmaceutically acceptable carrier:



wherein

R¹ is selected from H, C₁₋₆alkyl and benzyl;

5 R² is selected from H and C₁₋₆alkyl;

R³ is selected from H and C₁₋₆alkyl;

R⁴ is selected from C₁₋₆alkyl and halo;

R⁵ is selected from H and OH; and

and salts, solvates or hydrates thereof.

10

In another aspect of the invention, there are provided compositions containing the present compounds in amounts for pharmaceutical use to treat CNS conditions where a 5-HT_{1D}-like ligand is indicated. These and other aspects of the present invention are described in greater detail hereinbelow.

15

Detailed Description and Preferred Embodiments

The term "C₁₋₆alkyl" as used herein means straight and branched chain alkyl radicals containing from one to six carbon atoms and includes methyl, ethyl, propyl, 20 isopropyl, t-butyl and the like.

The term "halo" as used herein means halide and includes fluoro, chloro, bromo and iodo.

In embodiments of the invention, compounds of Formula I and II include those in which R¹ is selected from H, C₁₋₆alkyl and benzyl. In preferred embodiments, R¹ is H.

5 In another embodiment of the invention, compounds of Formula I and II include those in which R² and R³ are selected from H and C₁₋₆alkyl. In preferred embodiments, one of R² and R³ is H and the other is methyl or R² and R³ are both methyl.

10 In another embodiment of the invention, compounds of Formula I and II include those in which R⁴ is selected from C₁₋₆alkyl and halo. In preferred embodiments of the invention, R⁴ is selected from t-butyl, isopropyl and bromo. In the most preferred embodiment of the invention, R⁴ is t-butyl or isopropyl.

15 In a further embodiment of the invention, R⁵ is selected from H and OH; preferably, R⁵ is H.

In specific embodiments of the invention, the compounds of Formula I and Formula II include:

20

2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1H-imidazole;

2-[(4-t-butylphenyl)methyl]-4,5-dihydro-1H-imidazole;

2-[(4-bromo-2,6-dimethylphenyl)methyl]-1H-imidazole;

2-[(2,4,6-trimethylphenyl)methyl]-1H-imidazole;

25 2-[(2,6-dimethyl-4-isopropylphenyl)methyl]-1H-imidazole;

2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1-methylimidazole;

2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1-benzylimidazole;

2-[(4-t-butyl-2-methylphenyl)methyl]-1H-imidazole; and

2-[(4-t-butyl-2,6-dimethylphenyl-3-hydroxy)methyl]-1H-imidazole.

30

Preferred compounds of Formula I and II include:

- 2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1H-imidazole;
2-[(4-t-butylphenyl)methyl]-4,5-dihydro-1H-imidazole;
2-[(4-bromo-2,6-dimethylphenyl)methyl]-1H-imidazole;
2-[(2,4,6-trimethylphenyl)methyl]-1H-imidazole;
5 2-[(2,6-dimethyl-4-isopropylphenyl)methyl]-1H-imidazole;
2-[(4-t-butyl-2-methylphenyl)methyl]-1H-imidazole; and
2-[(4-t-butyl-2,6-dimethylphenyl-3-hydroxy)methyl]-1H-imidazole.

Particularly preferred compounds of Formula I and II include:

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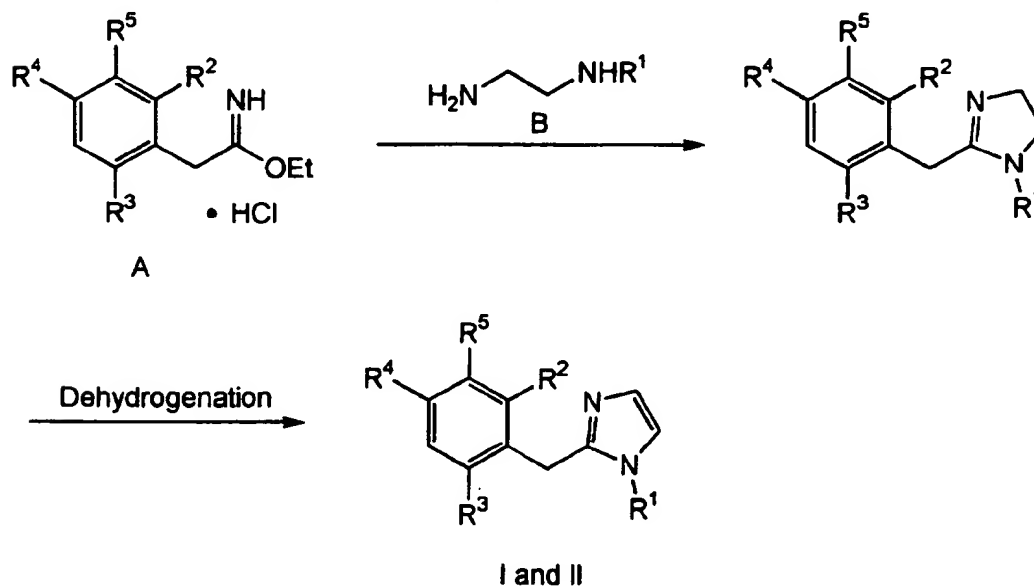
- 2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1H-imidazole;
2-[(4-t-butyl-2-methylphenyl)methyl]-1H-imidazole; and
2-[(2,6-dimethyl-4-isopropylphenyl)methyl]-1H-imidazole.

- 15 Acid addition salts of the compound of Formula I and II are most suitably formed from pharmaceutically acceptable acids, and include for example those formed with inorganic acids e.g. hydrochloric, sulphuric or phosphoric acids and organic acids e.g. succinic, maleic, acetic or fumaric acid. Other non-pharmaceutically acceptable salts e.g. oxalates may be used for example in the isolation of compounds of Formula I and
20 II for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt. Also included within the scope of the invention are solvates and hydrates of the invention.

- 25 The conversion of a given compound salt to a desired compound salt is achieved by applying standard techniques, in which an aqueous solution of the given salt is treated with a solution of base e.g. sodium carbonate or potassium hydroxide, to liberate the free base which is then extracted into an appropriate solvent, such as ether. The free base is then separated from the aqueous portion, dried, and treated with the requisite acid to give the desired salt.

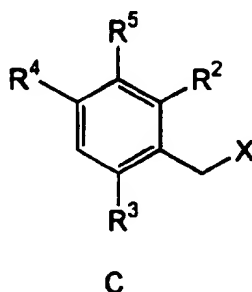
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The compounds of the present invention can be prepared by processes analogous to those established in the art. Therefore, compounds of Formula I and II wherein R^1 - R^5 are as defined above, can be prepared by coupling a reagent of Formula A with a reagent of Formula B in an alcoholic solvent such as ethanol at temperatures in the range of 25-100 °C, preferably at from 50-80 °C, followed by dehydrogenation of the intermediate imidazoline, as shown in the scheme below. This dehydrogenation reaction can be accomplished by heating the imidazoline with a catalyst like platinum, palladium or nickel in an inert solvent and under a stream of an inert gas. Preferred dehydrogenation conditions include using 10 palladium on carbon as catalyst in refluxing toluene under an atmosphere of nitrogen.



Reagents of Formula A can be prepared from the corresponding phenyl acetonitrile compound by treatment with ethanol in the presence of an appropriate acid such as hydrochloric acid in an inert solvent such as ether at temperatures in the range of 0 °C to 30 °C, preferably 0 °C to 25 °C. Reagents B are commercially available, and can be prepared using well established procedures known to one skilled in the art.

The phenyl acetonitrile precursors to Reagent A compounds are commercially available, and can be prepared from reagents of Formula C, wherein X is a leaving group such as a halogen or tosyl group, by treatment with sodium cyanide in a polar solvent at temperatures in the range of 50 to 100 °C. Preferred conditions are ethanol/water (6:1) at temperatures in the range of 75-100 °C.



15

Reagents of Formula C are commercially available, and can be synthesized by established techniques, for example by treating the alcohol with halogenating reagents such as CBr₄ and triphenylphosphine (X = Br) or thionyl chloride (X = Cl) in inert solvents such as methylene chloride and benzene.

20

The above alcohol precursor to reagents of Formula C are also commercially available, and can be prepared by reduction of the corresponding aldehyde using metal hydride reducing reagents in inert solvents such as ethanol, ether and tetrahydrofuran, at temperatures in the range of 0-70 °C. Preferred conditions for

reduction of the aldehyde are sodium borohydride in ethanol at temperatures in the range of 30-60 °C.

Most of the above aldehydes are commercially available, however, they also
5 can be prepared from the corresponding amines by displacement of the diazonium salt, prepared by reaction of the amine with sodium nitrite in the presence of an acid such as hydrochloric acid, with paraformaldehyde.

In an embodiment of the invention, the compound is provided in labeled
10 form, such as radiolabeled form, e. g. labeled by incorporation within its structure ^3H or ^{14}C or by conjugation to ^{125}I . In another aspect of the invention, the compounds in labeled form can be used to identify 5-HT_{1D}-like receptor ligands by techniques common in the art. This can be achieved by incubating the receptor in the presence of a ligand candidate and then incubating the resulting preparation
15 with an equimolar amount of radiolabeled compound of the invention such as [^3H]-2-[(2,6-dimethyl-4-isopropylphenyl)methyl]-1H-imidazole. 5-HT_{1D}-like ligands are thus revealed as those that are not significantly displaced by the radiolabeled compound of the present invention. Alternatively, 5-HT_{1D}-like ligand candidates may be identified by first incubating a radiolabeled form of a compound of the
20 invention then incubating the resulting preparation in the presence of the candidate ligand. A more potent 5-HT_{1D}-like ligand will, at equimolar concentration, displace the radiolabeled compound of the invention.

The present compounds are useful as pharmaceuticals for the treatment of
25 various conditions in which the use of a 5-HT_{1D}-like ligand is indicated, such as for the treatment of migraine, cluster headache and portal tension, a condition characterized by increased portal vein blood flow and typically associated with cirrhosis of the liver.

30 For use in medicine, the compounds of the present invention can be administered in a standard pharmaceutical composition. The present invention

therefore provides, in a further aspect, pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a Formula I or II compound or a pharmaceutically acceptable salt, solvate or hydrate thereof, in an amount effective to treat the target indication.

5

The compounds of the present invention may be administered by any convenient route, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions formulated accordingly.

10

Compounds of Formula I and II and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, or as solid forms such as tablets, capsules and lozenges. A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutical liquid carrier for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent. A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose. A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier, for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone,

lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilized and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as
5 aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container may be a unitary
10 dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer.

15

Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, wherein the active ingredient is formulated with a carrier such as sugar, acacia, tragacanth, or gelatin and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional
20 suppository base such as cocoa butter.

Preferably, the composition is in unit dose form such as a tablet, capsule or ampoule. Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 1 to 25 mg) of a
25 compound of Formula I or II or a pharmaceutically acceptable salt thereof calculated as the free base. The pharmaceutically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of from 1 mg to 500 mg, preferably between 10 mg and 400 mg, e.g., between 10 mg and 250 mg, or an intravenous, subcutaneous or intramuscular
30 dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g., between 1 mg and 25 mg, of a compound of Formula I or II or a pharmaceutically

acceptable salt, solvate or hydrate thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably, the compounds will be administered for a period of continuous therapy, for example for a week or more.

5 Example 1: 2,6-Dimethyl-4-isopropylbenzaldehyde

A solution of NaNO_2 (1.75 g, 25 mmol) in water (4 mL) was added to a stirred solution of 2,6-dimethyl-4-isopropylaniline hydrochloride (Schubert, W. M. *et al.* J. Amer. Chem. Soc. 1954, 76:1) (5 g, 25 mmol) in concentrated HCl (4.5 mL) at 0 °C.

10 The mixture was allowed to stir at 0 °C for 1.5 hours. Potassium acetate (6 g) was then added. At the same time, a solution of paraformaldehyde (1.15 g), hydroxylamine hydrochloride (2.63 g, 37.84 mmol) and potassium acetate (5.1 g) in water (17 mL) was heated under reflux for 15 min. To this solution, cooled to 10-15 °C, was added potassium acetate (16.5 g) in water (18 mL), copper sulfate (0.625 g) and sodium

15 sulfite (0.1 g). The neutral diazonium solution was then added immediately to the paraformaldehyde mixture and the resulting solution was allowed to stir at room temperature for 2 hours. The mixture was acidified with 20 mL of concentrated HCl and heated at reflux for 2 hours. The cooled mixture was extracted with ether (3 x 30 mL) and the solvent was removed under reduced pressure. The yellow liquid was purified

20 by column chromatography using as eluent hexane-EtOAc (97:3) to give 0.72 g (16%) of the title compound as a white liquid.

Example 2a: 2,6-Dimethyl-4-isopropylbenzyl alcohol

25 A solution of sodium borohydride (0.04 g, 1.04 mmol) in 90% ethanol (5 mL) was added dropwise to a solution of 2,6-dimethyl-4-isopropylbenzaldehyde (Example 1) (0.55 g, 3.1 mmol) in absolute ethanol (5 mL). The reaction mixture was allowed to stir at room temperature for 1 hour, then heated at 60 °C for 30 min. The solution was cooled to 0 °C and the unreacted sodium borohydride was decomposed by the addition

30 of a few drops of 3N HCl. The solvent was removed under reduced pressure to give a red oil which was suspended in water (10 mL) and extracted with ether (2 x 20 mL).

The ether was removed under reduced pressure to afford a red oil which was purified by flash chromatography using silica gel (eluted with hexane-EtOAc, 93:3) to give 0.48 g (87%) of the title compound as a white solid; mp 75-77 °C.

5 In a like manner, the following additional compound was prepared:

(b) 4-Bromo-2,6-dimethylbenzyl alcohol, from 4-bromo-2,6-dimethylbenzaldehyde (Hjed, H. et al. Acta Chem. Scand. 1965, 19:2166); 95% yield, mp 117-119 °C.

Example 3a: 2,6-Dimethyl-4-isopropylbenzyl chloride

Thionyl chloride (0.63 g, 5.28 mmol) was added to a solution of 2,6-dimethyl-4-isopropylbenzyl alcohol (Example 2a) (0.47 g, 2.64 mmol) in dry benzene (20 mL). The reaction mixture was allowed to stir at room temperature for 2 hours. The solvent was removed under reduced pressure to give a yellow oil. The crude oil was suspended in water (10 mL) and extracted with ether (3 x 10 mL). The solvent was removed under reduced pressure to give 0.51 g (98%) of the title compound as a white liquid.

In a like manner, the following additional compound was prepared:

(b) 4-Bromo-2,6-dimethylbenzyl chloride, from 4-bromo-2,6-dimethylbenzyl alcohol (Example 2b); white solid, 95% yield, mp 63-65 °C.

(c) 4-t-Butyl-2-methylbenzylchloride, from 4-t-butyl-2-methylbenzyl alcohol (Baciocchi, E. et al. Tetrahedron, 1988, 44:6525).

15

Example 4a: 4-t-Butylphenylacetonitrile

Sodium cyanide (1.07 g, 22 mmol) was added to a stirred solution of 4-t-butylbenzylbromide (5 g, 22 mmol) in a mixture of EtOH-H₂O (6:1) (70 mL). The reaction mixture was allowed to stir under reflux conditions for 4 hours. After cooling the mixture to room temperature, the solvent was evaporated under reduced pressure to afford a yellow oil. The oil was suspended in water (20 mL) and extracted with ether (3 x 25 mL). The solvent was removed under reduced pressure to give a yellow oil which was purified by distillation (Kugelrohr, bp 120-125 °C, 0.2 mm Hg) to afford 3.37 g (89%) of the title compound as a colorless oil.

In a like manner the following addition compounds were prepared:

(b) 2,4,6-Trimethylphenylacetonitrile, from 2,4,6-trimethylbenzyl chloride.

(c) 2,6-Dimethyl-4-isopropylphenylacetonitrile, from 2,6-dimethyl-4-isopropylbenzyl chloride (Example 3a); 64% yield, mp 58-60 °C.

(d) 4-Bromo-2,6-dimethylphenylacetonitrile, from 4-bromo-2,6-dimethylbenzyl chloride (Example 3b); white solid, 75% yield, mp 83-85 °C.

(e) 4-t-Butyl-2-methylphenylacetonitrile, from 4-t-butyl-2-methylbenzylchloride (Example 3c); oil, bp 135-140 °C.

Example 5a: 2-[(2,6-Dimethyl-4-isopropylphenyl)methyl]-4,5-dihydro-1H-imidazole hydrochloride

To a solution of 2,6-dimethyl-4-isopropylphenylacetonitrile (Example 4c); (0.2 g, 1.07 mmol) in anhydrous ether (20 mL) was added absolute ethanol (0.05 g, 1.07 mmol) and an excess of HCl gas was passed into the solution with cooling in an ice bath. The resulting solution was allowed to stir at 0 °C for 2 hours and kept in a refrigerator for 4 days. The white solid was collected by filtration, washed with ether (2 x 5 mL) and dried to give 0.12 g (42%) of 2-(2,6-dimethyl-4-isopropylphenyl)acetimidate hydrochloride as a white solid, mp 231-233 °C. A solution of ethylenediamine (0.053 g, 0.89 mmol) in absolute ethanol (1 mL) was added to a solution of the imidate hydrochloride (0.12 g, 0.44 mmol) in absolute ethanol (4 mL) cooled at ice-bath temperature. After stirring at 0 °C for 2 hour, the solution was heated at reflux for 20 minutes. The solvent was evaporated and the oily residue was washed with water (2 x 1 mL) and extracted with methylene chloride (3 x 10 mL). The solution was dried (MgSO₄), filtered and evaporated under reduced pressure to afford the free base of the title compound as a white solid (mp 112-114 °C). A solution of the free base in anhydrous ether was treated with dry HCl gas. The crude salt was collected and recrystallized from ethanol/ether to give 0.08 g (65%) of the title compound as a white solid. mp 296-298 °C; Anal. C₁₅H₂₂N₂·HCl·0.1H₂O: C, H, N.

25

In a like manner, the following additional compounds were prepared:

- (b) 2-[(4-t-Butylphenyl)methyl]-4,5-dihydro-1H-imidazole hydrochloride, from 4-t-butylphenylacetonitrile (Example 4a); white crystals, mp 232-234 °C, Anal.
- 5 C₁₄H₂₀N₂·HCl: C, H, N.
- (c) 2-[(4-t-Butyl-2,6-dimethylphenyl)methyl]-4,5-dihydro-1H-imidazole hydrochloride, from 4-t-butyl-2,6-dimethylphenylacetonitrile (Bun-Hoi *et al.* Bull. Soc. Chim. 1942, 9:889); white solid, mp 327-329 °C.
- (d) 2-[(4-Bromo-2,6-dimethylphenyl)methyl]-4,5-dihydro-1H-imidazole
- 10 hydrochloride, from 4-bromo-2,6-dimethylphenylacetonitrile (Example 4d); white solid, mp 293-295 °C, Anal. C₁₂H₁₅BrN₂·HCl: C, H, N.
- (e) 4,5-Dihydro-2-[(2,4,6-trimethylphenyl)methyl]-1H-imidazole hydrochloride, from 2,4,6-trimethylphenylacetonitrile (Example 4b); white solid, 63% yield, mp 274-276 °C.
- 15 (f) 2-[(4-t-Butyl-2,6-dimethylphenyl)methyl]-4,5-dihydro-1-methylimidazole hydrochloride, from 4-t-butyl-2,6-dimethylphenylacetonitrile (Bun-Hoi *et al.* Bull. Soc. Chim. 1942, 9:889) and N-methylethylenediamine; white solid, 73% yield, mp 250-252 °C, Anal. C₁₇H₂₈N₂·HCl: C, H, N.
- (g) 2-[(4-t-Butyl-2,6-dimethylphenyl)methyl]-4,5-dihydro-1-benzylimidazole
- 20 hydrochloride, from 4-t-butyl-2,6-dimethylphenylacetonitrile and N-benzylethylenediamine; white solid, 68% yield, mp 216-218 °C, Anal. C₂₃H₃₀N₂·HCl: C, H, N.
- (h) 2-[(4-t-Butyl-2-methylphenyl)methyl]-4,5-dihydro-1H-imidazole hydrochloride, from 4-t-butyl-2-methylphenylacetonitrile (Example 4e); white
- 25 solid, mp 255 °C, Anal. C₁₅H₂₂N₂·HCl·0.25H₂O: C, H, N.

Example 6a: 2-[(4-t-Butyl-2,6-dimethylphenyl)methyl]-1H-imidazole oxalate

A suspension of 2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-4,5-dihydro-1H-

30 imidazole (free base of Example 5c) (0.1 g, 0.4 mmol) and 10% Pd-C (0.1 g) in toluene (10 mL) was refluxed under a nitrogen atmosphere for 3 days. The catalyst

was removed by filtration and the filtrate was concentrated under reduced pressure to give 2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1H-imidazole (0.085 g) as a white solid. The oxalate salt was prepared and recrystallized from MeOH/Et₂O to afford the title compound as white crystals (0.088 g, 66%). mp 154-156 °C, Anal.

5 $C_{16}H_{22}N_2 \cdot C_2H_2O_4$: C, H, N.

In a like manner, the following additional compounds were prepared:

- (b) 2-[(4-Bromo-2,6-dimethylphenyl)methyl]-1H-imidazole hydrochloride, from 2-
10 [(4-bromo-2,6-dimethylphenyl)methyl]-4,5-dihydro-1H-imidazole (Example 5d);
61%; mp 276-278 °C, Anal. $C_{12}H_{13}BrN_2 \cdot HCl \cdot 0.25H_2O$: C, H, N.
- (c) 2-[(4-t-Butyl-2,6-dimethylphenyl)methyl]-1-benzylimidazole hydrochloride,
from 2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-4,5-dihydro-1-benzylimidazole
(Example 5g); 6%, mp 229-231 °C, Anal. $C_{23}H_{28}N_2 \cdot HCl$: C, H, N.
- 15 (d) 2-[(4-t-Butyl-2,6-dimethylphenyl)methyl]-1-methylimidazole hydrochloride,
from 2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-4,5-dihydro-1-methylimidazole
(Example 5f); 61%, mp 231-233 °C, Anal. $C_{17}H_{24}N_2 \cdot HCl$: C, H, N.
- (e) 2-[(4-t-Butylphenyl)methyl]-1H-imidazole hydrochloride, from 2-[(4-t-
butylphenyl)methyl]-4,5-dihydro-1H-imidazole (Example 5b); 82%, mp 192-194
20 °C, Anal. $C_{14}H_{18}N_2 \cdot HCl$: C, H, N.
- (f) 2-[(2,4,6-Trimethylphenyl)methyl]-1H-imidazole hydrochloride, from 4,5-
dihydro-2-[(2,4,6-trimethylphenyl)methyl]-1H-imidazole (Example 5e); 75%, mp
235-237 °C, Anal. $C_{13}H_{16}N_2 \cdot HCl \cdot 0.2H_2O$: C, H, N.
- (g) 2-[(2,6-Dimethyl-4-isopropylphenyl)methyl]-1H-imidazole hydrochloride, from
25 2-[(2,6-dimethyl-4-isopropylphenyl)methyl]-4,5-dihydro-1H-imidazole (Example
5a); 70%, mp 278-280 °C, Anal. $C_{15}H_{20}N_2 \cdot HCl$: C, H, N.
- (h) 2-[(4-t-Butyl-2,6-dimethylphenyl-3-hydroxy)methyl]-1H-imidazole
hydrochloride, from 2-[(4-t-butyl-2,6-dimethylphenyl-3-hydroxy)methyl]-4,5-
dihydro-1H-imidazole (oxymetazoline, see Merck Index, 11th ed. 6919); 41%,
30 mp 276-278 °C, Anal. $C_{16}H_{22}N_2O \cdot HCl \cdot 0.5H_2O$: C, H, N.

- (i) 2-[(4-t-Butyl-2-methylphenyl)methyl]-1H-imidazole, from 2-[(4-t-butyl-2-methylphenyl)methyl]-4,5-dihydro-1H-imidazole (Example 5h).

Example 7: Agonist Assay

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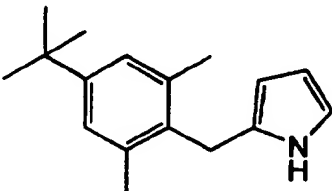
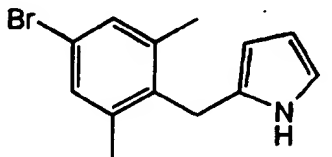
The *in vitro* evaluation of the 5-HT_{1D}-like receptor agonist activity of the compounds of the invention was carried out by testing the extent to which they mimic sumatriptan in contracting the rabbit saphenous vein (Perez, M. *et al.* J. Med. Chem. 1995, 38:3602-3607).

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Tissues were obtained from male New Zealand White rabbits (~3-4 kg) which were sacrificed by an overdose of pentobarbital. The saphenous veins from both the left and right side were cleaned of fat and connective tissue and placed in Krebs solution (118 mM NaCl, 11 mM glucose, 25 mM NaHCO₃, 4.7 mM KCl, 2.5 mM CaCl₂·2H₂O, 1.2 mM KH₂PO₄, and 1.2 mM MgSO₄·7H₂O. Ring segments of the vein (4-5 mm in length) were cut and the endothelium gently removed. The segments were mounted in 10 mL baths containing Krebs buffer and were constantly aerated with 95% oxygen/5% carbon dioxide and maintained at 37°C and pH 7.4 in order to record the isometric tension. A resting tension of 2.5 g was applied and the tissues allowed to equilibrate for 90 minutes, with washing every 15-20 minutes. After the equilibrium period, the rings were depolarized by the addition of two aliquots of KCl (80 mM final concentration) separated by a 20 minute washing period. The tissues were then exposed to prazosin, idazoxan and indomethacin (all 1 mM final concentration) for 30 minutes in order to exclude the actions of α₁- and α₂-adrenergic receptors and prostaglandin receptors respectively. Cumulative concentration-effect curves were then constructed for sumatriptan and the test compounds. Responses were calculated as a percentage of the maximal contraction evoked by 80 mM KCl. Only one compound was tested per preparation.

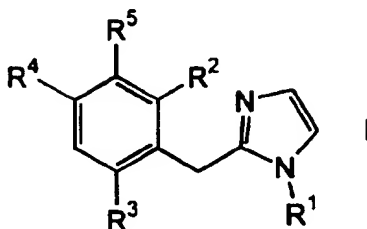
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The following Table illustrates the in vitro activities for the compounds of the invention on the rabbit isolated saphenous vein. EC_{50} represents the concentration of the compound which causes 50% of the maximum contraction effected by it.

5	Compound	EC_{50} (mM)
	sumatriptan	0.22
		0.13
		9.3

We Claim:

1. A compound according to Formula I and salts, solvates or hydrates thereof:



wherein

R¹ is selected from H, C₁₋₆alkyl and benzyl;

R² is selected from H and C₁₋₆alkyl;

R³ is selected from H and C₁₋₆alkyl;

R⁴ is selected from C₁₋₆alkyl and halo;

R⁵ is selected from H and OH; and

with the proviso that when R¹ is H and R² and R³ are methyl, R⁴ is not t-butyl.

2. A compound according to claim 1, wherein R¹ is H.
3. A compound according to claim 1, wherein R² and R³ are selected from H and methyl.
4. A compound according to claim 3, wherein R² and R³ are methyl.
5. A compound according to claim 1, wherein R⁴ is selected from bromo, t-butyl and isopropyl.

6. A compound according to claim 5, wherein R² and R³ are methyl.

7. A compound according to claim 1, wherein R⁵ is H.

8. A compound according to claim 5, wherein R⁵ is H.

9. A compound according to claim 1, selected from

2-[(4-t-butylphenyl)methyl]-4,5-dihydro-1H-imidazole;
2-[(4-bromo-2,6-dimethylphenyl)methyl]-1H-imidazole;
2-[(2,4,6-trimethylphenyl)methyl]-1H-imidazole;
2-[(2,6-dimethyl-4-isopropylphenyl)methyl]-1H-imidazole;
2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1-methylimidazole;
2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1-benzylimidazole;
2-[(4-t-butyl-2-methylphenyl)methyl]-1H-imidazole; and
2-[(4-t-butyl-2,6-dimethylphenyl-3-hydroxy)methyl]-1H-imidazole.

10. A compound according to claim 9, selected from

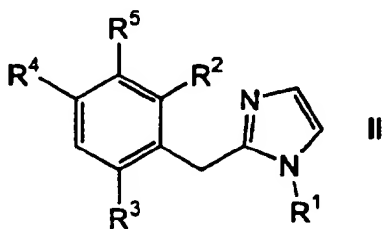
2-[(4-t-butylphenyl)methyl]-4,5-dihydro-1H-imidazole;
2-[(4-bromo-2,6-dimethylphenyl)methyl]-1H-imidazole;
2-[(2,4,6-trimethylphenyl)methyl]-1H-imidazole;
2-[(2,6-dimethyl-4-isopropylphenyl)methyl]-1H-imidazole;
2-[(4-t-butyl-2-methylphenyl)methyl]-1H-imidazole; and
2-[(4-t-butyl-2,6-dimethylphenyl-3-hydroxy)methyl]-1H-imidazole.

11. A compound according to claim 10, selected from

2-[(2,6-dimethyl-4-isopropylphenyl)methyl]-1H-imidazole; and

2-[(4-t-butyl-2-methylphenyl)methyl]-1H-imidazole.

12. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and, in an amount effective to stimulate a 5-HT_{1D}-like receptor, a compound according to Formula II:



wherein

R¹ is selected from H, C₁₋₆alkyl and benzyl;

R² is selected from H and C₁₋₆alkyl;

R³ is selected from H and C₁₋₆alkyl;

R⁴ is selected from C₁₋₆alkyl and halo;

R⁵ is selected from H and OH; and salts, hydrates and solvates thereof.

13. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and, in an amount effective to stimulate a 5-HT_{1D}-like receptor, a compound according to claim 2.

14. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and, in an amount effective to stimulate a 5-HT_{1D}-like receptor, a compound according to claim 5.

15. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and, in an amount effective to stimulate a 5-HT_{1D}-like receptor, a compound according to claim 7.

16. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and, in an amount effective to stimulate a 5-HT_{1D}-like receptor, a compound selected from

2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1H-imidazole;
2-[(4-t-butylphenyl)methyl]-4,5-dihydro-1H-imidazole;
2-[(4-bromo-2,6-dimethylphenyl)methyl]-1H-imidazole;
2-[(2,4,6-trimethylphenyl)methyl]-1H-imidazole;
2-[(2,6-dimethyl-4-isopropylphenyl)methyl]-1H-imidazole;
2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1-methylimidazole;
2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1-benzylimidazole;
2-[(4-t-butyl-2-methylphenyl)methyl]-1H-imidazole; and
2-[(4-t-butyl-2,6-dimethylphenyl-3-hydroxy)methyl]-1H-imidazole.

17. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and, in an amount effective to stimulate a 5-HT_{1D}-like receptor, a compound selected from

2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1H-imidazole;
2-[(4-t-butylphenyl)methyl]-4,5-dihydro-1H-imidazole;
2-[(4-bromo-2,6-dimethylphenyl)methyl]-1H-imidazole;

2-[(2,4,6-trimethylphenyl)methyl]-1H-imidazole;
2-[(2,6-dimethyl-4-isopropylphenyl)methyl]-1H-imidazole;
2-[(4-t-butyl-2-methylphenyl)methyl]-1H-imidazole; and
2-[(4-t-butyl-2,6-dimethylphenyl-3-hydroxy)methyl]-1H-imidazole.

18. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and, in an amount effective to stimulate a 5-HT_{1D}-like receptor, a compound selected from

2-[(4-t-butyl-2,6-dimethylphenyl)methyl]-1H-imidazole;
2-[(4-t-butyl-2-methylphenyl)methyl]-1H-imidazole; and
2-[(2,6-dimethyl-4-isopropylphenyl)methyl]-1H-imidazole.

19. A method for treating a patient having a medical condition for which a 5-HT_{1D}-like receptor agonist is indicated, comprising the step of administering to the patient a pharmaceutical composition as defined in claim 12.

20. A method for treating a patient according to claim 19, wherein the medical condition is migraine.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 97/00680

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D233/54 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	M. DROST ET AL.: CAN. SOC. FORENS. SCI. J., vol. 22, no. 4, 1989, pages 311-5, XP002049617 see page 313, figure 3, "Imidazole metabolite"; page 314, figure 4 ---	1
A	DE 35 02 508 A (GLAXO GROUP LTD.) 14 August 1985 see page 6, line 26 - page 8, line 15; claims 1,11 ---	1,12
A	EP 0 266 899 A (GLAXO GROUP LTD.) 11 May 1988 see page 4, line 50 - line 54 --- -/--	1,12

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *S* document member of the same patent family

Date of the actual completion of the international search

9 December 1997

Date of mailing of the international search report

18.12.97

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Hass, C

INTERNATIONAL SEARCH REPORT

Intern. Patent Application No.

PCT/CA 97/00680

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>M. PEREZ ET AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, 1995, pages 3602-7, XP002049618 cited in the application see figure 1; table 1 -----</p>	1,12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 97/00680

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/CA 97/00680

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 19,20

because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Remark : Although claims 19 and 20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 97/00680

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 3502508 A	14-08-85	AT 392276 B	25-02-91
		AU 579132 B	17-11-88
		AU 3809785 A	01-08-85
		BE 901576 A	25-07-85
		CA 1252793 A	18-04-89
		CH 664152 A	15-02-88
		CY 1479 A	21-07-89
		DK 35785 A	26-07-85
		FR 2561244 A	20-09-85
		GB 2153821 A,B	29-08-85
		HK 33189 A	28-04-89
		JP 1720916 C	24-12-92
		JP 3078862 B	17-12-91
		JP 60214784 A	28-10-85
		LU 85743 A	04-08-86
		LU 88268 A	03-02-94
		NL 8500202 A,B,	16-08-85
		SE 460359 B	02-10-89
		SE 8500368 A	26-07-85
		SK 404391 A	09-08-95
		US 4695578 A	22-09-87
EP 266899 A	11-05-88	JP 63146874 A	18-06-88
		US 4814344 A	21-03-89